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21 July 2005

Food and Drug Administration
Division of Dockets Management (HFA-305)
Room 1061
5630 Fishers Lane
Rockville, MD 20852

RE: Comments to Docket No. 2005D-0183
Draft Guidance for Industry on Antiviral Drug Development
GSI Ref. No. 012

Sir or Madam:

Gilead Sciences, Inc. (Gilead) hereby submits comments on the Draft Guidance for Industry titled "Antiviral Drug Development—Conducting Virology Studies and Submitting the Data to the Agency" (Docket No. 2005D-0183).

Two copies of the document are provided as required.

Please contact me at (650) 522-5093 or by facsimile at (650) 522-5489 if you have any questions or need additional information. You may also contact Pamela Danagher, Associate Director, Regulatory Affairs at (650) 522-6395. We share the same facsimile number.

Sincerely,

Christophe Beraud, Ph.D.
Senior Associate, Regulatory Affairs

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Food and Drug Administration
Docket 2005D-0183

Comments on Draft Guidance for Industry titled "Antiviral Drug Development--Conducting Virology Studies and Submitting the Data to the Agency" May 2005

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21 July 2005

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1. INTRODUCTION

Gilead Sciences, Inc. (Gilead) hereby submits comments on the Draft Guidance for Industry titled "*Antiviral Drug Development--Conducting Virology Studies and Submitting the Data to the Agency*".

Gilead appreciates the Food and Drug Administration's (the Agency's) efforts to provide the industry with clear guidance regarding the nature of virology nonclinical and clinical studies supporting antiviral drug development, including the format of the virology reports to be submitted to the agency. While recognizing that the document prepared by the Division of Antiviral Drug Products (the Division) represents the Agency's current thinking on the topic, provided here are additional considerations and suggested clarifications for inclusion in the final guidance.

2. ORGANIZATION OF THE COMMENTS

Comments on specific sections of the draft guidance document are provided in the order in which they appear in the document issued by the Agency. Reference to the section number, page number and line number of the document is made for each comment. In addition, excerpts from the draft guidance referred to in the comments are provided in italic font.

3. GILEAD'S COMMENTS

3.1. Section III-Nonclinical Virology Reports, B-Recommended Components of Nonclinical Virology Reports, 3-Cytotoxicity/Therapeutic Index

Page 7, Lines 270-272

Therefore, it is important to monitor the effects of certain investigational drugs (e.g., nucleoside analogs) on mitochondrial toxicity by examining mitochondrial morphology, glucose utilization, lactic acid production, and mitochondrial DNA content.

The use of the standard assays of lactic acid production and mitochondrial DNA content is warranted for characterizing potential mitochondrial toxicity of investigational drugs such as nucleoside analogs. However, in the absence of mitochondrial toxicity signals from these assays, mitochondrial morphology and glucose utilization assays do not provide additional significant information. Gilead proposes for consideration that the mitochondrial morphology and glucose utilization assays be second tier assays performed when the standard lactic acid production and mitochondrial DNA content assays indicate a potential for mitochondrial toxicity or when these assays provide ambiguous results.

3.2. Section III-Nonclinical Virology Reports, B-Recommended Components of Nonclinical Virology Reports, 4-In Vitro Combination Activity Analysis

Page 7, Lines 281-283

For this reason, we recommend that sponsors evaluate the in vitro antiviral activity of investigational drugs in two- or three-drug combinations with other drugs approved for the same indication.

With an increasingly large number of drugs approved for the treatment of HIV, HBV and HCV infection, the number of possible combinations is gradually becoming excessive for in vitro antiviral activity analyses. Gilead recommends that consideration be given to testing only two-drug combinations of widely used drugs and/or representatives from each drug class. Three-drug combinations are difficult to assess in in vitro antiviral activity assays. Indeed, the strong antiviral activity of three-drug combinations does not permit adequate concentrations of all three drugs for detection of antagonistic or synergistic effects. Therefore, two-drug combinations antiviral analyses are more revealing in assessing the potential for synergistic effects and furthermore can be readily conducted for clinically relevant drug combinations.

3.3. Section III-Nonclinical Virology Reports, B-Recommended Components of Nonclinical Virology Reports, 5-Resistance, a-Selection of Resistant Virus In Vitro

Page 8, Lines 319-323

Sponsors are encouraged to assess the development of resistance in vitro over the concentration range spanning the anticipated in vivo concentration and to determine if the same or different patterns of resistance mutations develop by repeating the selection of variants resistant to the investigational drug several times.

The conduct of long term experiments to characterize the development of in vitro resistance to an investigational drug is often challenging from a technical standpoint. Gilead's experience with such experiments is that conducting duplicate selections is usually sufficient to determine in vitro resistance patterns. Gilead recommends that the Agency consider including reference to duplicate selection experiments for the purpose of characterizing the emergence of resistance to an investigational drug in vitro.

3.4. Section III-Nonclinical Virology Reports, B-Recommended Components of Nonclinical Virology Reports, 5-Resistance, b-Genotypic Analysis

Page 8, Lines 347-351

In the case of larger viruses, we suggest that the relevant portions of the viral gene targeted by the investigational agent be sequenced and analyzed for mutations that could contribute to drug resistance. It is preferable to characterize resistance pathways in several genetic backgrounds (i.e. strains, subtypes, genotypes) and to obtain isolates during the selection process to identify the order in which multiple mutations appear.

It would be helpful if the Agency provided additional guidance as to what constitutes a large virus such as providing the genome size above which a virus would be considered to be large or by specifically providing examples of viruses that the Agency considers as large.

In addition, given that there are numerous strains, subtypes and genotypes of HIV-1, HBV and HCV, it would be helpful if the Agency provided additional guidance with respect to the genetic backgrounds that should be used by the sponsor in an effort to characterize resistance pathways. Gilead would recommend that in vitro data from the most common subtypes or genotypes of viruses that will be studied in clinical trials be provided.

3.5. Section III-Nonclinical Virology Reports, B-Recommended Components of Nonclinical Virology Reports, 5-Resistance, d-Cross-resistance

Page 10, Lines 412-415

We recommend that multiple clinical isolates be examined by phenotypic assays with the investigational drug and clinical isolates representative of the breadth of diverse mutations and combinations known (if known) to confer reduced susceptibility.

The state-of-the-art phenotyping technologies utilize modern recombinant approaches to generate viruses to determine drug IC_{50} values against panels of viral strains. A number of commercial assays have been developed (such as ViroLogic and Virco assays) that have been widely and successfully used throughout the industry. These *recombinant* clinical isolates contain the target gene sequence in the context of consistent background allowing for reproducible and accurate comparison of the data across independent experiments. Data from primary clinical isolates, due to the nature of the individual isolated, will be necessarily more limited. Gilead would recommend that the Agency consider that a combination of data from recombinant and primary clinical isolates would be acceptable for characterization of cross-resistance.

3.6. Section IV-Proposal for Monitoring Resistance Development

Page 11, Lines 465-467

Sponsors are strongly encouraged to collect (at a minimum) phenotype and genotype data for baseline isolates from all patients and endpoint isolates from all virologic failures and discontinuations (not suppressed).

As currently written, this section suggests that baseline genotypes and phenotypes should be collected on all patients enrolling in the clinical trials. This language is inconsistent with the language on Page 13, Lines 529-530, which describes the requirements for baseline phenotypic data as limited to patients with virologic failure and discontinuations (not suppressed). Gilead agrees that collecting baseline genotypic data from all study participants is necessary to determine the presence of possible baseline resistance mutations even among treatment-naïve patients.

While collecting baseline phenotypic data on all study participants might appear to be a comprehensive approach to characterize resistance during drug development, Gilead does not believe that this systematic approach is always scientifically justified for the following reasons:

- In treatment-naïve patients, phenotypic data for proven drug classes such as reverse transcriptase inhibitors or protease inhibitors does not yield a sufficient range of variability (< 3 fold) to warrant testing of all patients at baseline. In phase 3 clinical studies of treatment-naïve patients, an approach based on baseline genotyping of all patients followed by phenotyping of samples with possible resistance would provide as

much valuable information in terms of characterizing the relationship between genotype/phenotype and virologic response to the drug.

- For some classes of drugs such as HIV entry inhibitors or fusion inhibitors, there is a higher variability among treatment-naive patients. In this instance, the sample size for phenotypic analyses should be guided by statistical considerations in order to gather sufficient data to establish the efficacy of the test drug. In the case of poorly-characterized new drug classes, the sponsor should establish a plan during the drug development program to evaluate the variability of the drug response in treatment-naïve patients based on statistical approaches.

- Similarly, for treatment-experienced patients, a sufficient sample size should be determined to allow prediction of clinically relevant breakpoints for drug activity. In both cases, phenotypic data from every patient enrolled in a study may not be necessary to support robust conclusions, and therefore the size of the sample for phenotypic analyses should be determined based on statistical considerations.

Also, it should considered that discontinuations prior to week 8 of treatment be exempt from virologic failure analysis since virologic suppression would not be expected that early after the initiation of therapy and/or plasma samples may not be collected for such analysis.

3.7. Appendix 1-Template for Submitting HIV Resistance Data, V.-Phenotypic Data

Page 15, Lines 605-613

- *Approved/investigational anti-HIV agents (List first agents in the same class in alphabetical order followed by agents with the same target protein in alphabetical order. End with agents outside drug class in alphabetical order.)*
  – *Fold change in IC_{50} value of baseline compared to reference strain for all approved/investigational anti-HIV agents*
  – *Fold change in IC_{50} value at time of endpoint assessment or failure compared to reference strain for each of the approved/investigational anti-HIV agents*
  – *Fold change in IC_{50} value at time of endpoint assessment or failure compared to baseline for each of the approved/investigational anti-HIV agents*

While Gilead acknowledges the importance of providing phenotypic data for approved drugs, access to investigational drugs not being evaluated by the sponsor is often limited, thereby precluding the conduct of experiments with such agents. Gilead recommends that the Agency consider incorporating language indicating that phenotypic experiments with investigational drugs should be conducted if the drug is readily available to the sponsor.